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Sir:

Transmitted herewith for filing is the patent application of

Inventor(s): Steve A. Herweck, et al.

For: Expandable Fluoropolymer Device For Delivery of Therapeutic Agents and Method of Making

Enclosed are:

- ☐ This is a request for filing a ☐ continuation ☐ divisional application under 37 CFR 1.53(b), of pending prior application serial no. _____ filed on _____ entitled _____.
- ☒ 30 pages of specification, 9 pages of claims, 1 pages of abstract.
- ☒ 12 sheets of drawings.
- ☒ A Declaration, Petition and Power of Attorney. (unexecuted)
- ☐ An assignment of the invention to _____ A recordation form cover sheet (Form PTO 1595) is also enclosed.
- ☐ A verified statement to establish small entity status under 37 C.F.R. 1.9 and 37 C.F.R. 1.27.
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TOTAL CLAIMS	52 - 20 =	32
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RATE	FEE
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x 9=	\$ 288
x 39	\$ 195
+130	\$
TOTAL	\$862.00

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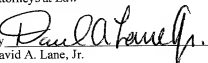
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Lahive & Cockfield, LLP
 28 State Street
 Boston, Massachusetts 02109

Date: October 1, 1999

LAHIVE & COCKFIELD, LLP
 Attorneys at Law

By 
 David A. Lane, Jr.
 Reg. No. 39,261
 28 State Street
 Boston, MA, 02109
 (617) 227-7400
 Telecopier (617) 742-4214

EXPANDABLE FLUOROPOLYMER DEVICE FOR DELIVERY OF THERAPEUTIC AGENTS AND METHOD OF MAKING

Reference to Related Applications

This application claims priority to Provisional Application Serial Number 60/117,152, filed January 25, 1999, and incorporated herein by reference.

Background of the Invention

Catheter delivered inflatable balloons are utilized in a wide range of surgical procedures to dilate, obstruct, or restore patency to body vessels and organs, as well as to maintain the position of catheter delivered instruments in vivo. Such balloons are typically attached to the distal tip of a small diameter catheter tube to facilitate delivery of the balloon to a treatment site within the body. The balloon is advanced by the catheter through a body vessel while in a deflated condition until the balloon is appropriately positioned proximate the treatment site. The balloon is inflated by infusing a fluid, such as saline, a contrast media, or water, into the balloon through an inflation lumen provided in the catheter. The inflated balloon is deflated after treatment and subsequently removed from the body.

Perforated and porous catheter balloons have been proposed to deliver therapeutic agents, e.g. drugs and other medicinal agents, directly to the treatment site while concomitantly performing their primary function of dilation, obstruction, etc. The localized delivery of therapeutic agents to the treatment site can increase the effectiveness of the therapeutic agent and minimize or even negate the systemic side effects of the agent. Generally, the therapeutic agent is delivered through the wall of the catheter either through openings mechanically formed in the wall or through pores present in the material used to form the balloon. A problem common to such conventional catheter balloons is that the flow-rate and the uniform delivery of fluid, and hence the therapeutic agent, through the walls of the balloon is difficult to control. Successful delivery of the therapeutic agent to the treatment site requires the therapeutic agent to penetrate the body tissue at the treatment site to a depth sufficient for the agent to effect the treatment site without effecting healthy tissue or organs proximate the tissue site. For this reason, the flow rate of and the uniform delivery of the therapeutic agent

through the walls of the balloon is important. If the flow rate is too low, the therapeutic agent can fail to properly penetrate the tissue at treatment site. If the flow rate is too high, the therapeutic agent can be delivered to areas of the body outside of the treatment area and, in some cases, elevated flow rates can result in the formation of high velocity fluid jets which can traumatize the tissue adjacent the walls of the balloon.

Summary of the Invention

The present invention provides a radially expandable fluid delivery device for delivering fluid to a treatment site within the body. The radially expandable fluid delivery device can be used, for example, as a catheter delivered balloon for the treatment of body lumens, organs, and grafts. Fluids, including therapeutic agents, can be delivered through the walls of the fluid delivery device to effect localized treatment of sites within the body. The fluid delivery device of the present invention is constructed of a biocompatible material having a microstructure that can provide a controlled, uniform, low-velocity distribution of fluid through the walls of the fluid delivery device to effectively deliver the fluid to the treatment site without damaging tissue proximate the walls of the device.

In accordance with one aspect of the present invention, the fluid delivery device comprises a member constructed of a biocompatible material. The member is defined by a wall having a thickness extending between an inner and an outer surface. The wall is characterized by a microstructure of nodes interconnected by fibrils. The member is deployable from a first, reduced diameter configuration to a second, increased diameter configuration upon the introduction of a pressurized fluid to the lumen. The member includes at least one microporous portion having a porosity sufficient for the pressurized fluid to permeate through the wall. The spaces between the nodes control the permeation of fluid through the wall of the fluid delivery device. In a preferred embodiment, substantially all of the nodes within the microporous portion are oriented such that spaces between the nodes form generally aligned micro-channels extending from the inner surface to the outer surface of the wall.

In accordance with another aspect of the present invention, the nodes within the microporous portion of the member can be oriented substantially parallel to the

longitudinal axis of the member. The micro-channels are preferably sized to permit the passage of the pressurized fluid from the inner surface to the outer surface of the wall. The size of the microchannels within the microporous portion can be varied longitudinally and/or circumferentially to provide regions of increased porosity within the microporous portion. The presence of regions of differing porosity allows the volume of fluid delivered through the microporous portion of the member to vary, longitudinally and/or circumferentially, across the microporous portion. This allows the microporous portion to be specifically tailored to the size and shape of the site being treated.

Various biocompatible materials are suitable for the construction of the member. Expanded polytetrafluoroethylene (ePTFE), which is a hydrophobic, biocompatible, inelastic material having a low coefficient of friction, is the preferred material of choice.

In accordance with a further aspect of the present invention, the member can be provided with first and second microporous portions, each having a porosity sufficient for the pressurized fluid to permeate through the wall of the member. The first and second microporous portions can be spaced apart longitudinally and/or circumferentially. An impermeable or semi-permeable portion can be interposed between the first and second microporous portions. Further microporous portions and/or impermeable or semi-permeable portions can also be provided on the member. The microporous portions and the impermeable portions can be arranged in numerous alternative configurations. For example, microporous ring-shaped portions can be spaced along the longitudinal axis of the member. Alternatively, the microporous portions can be generally rectangular in shape and can be spaced apart about the circumference of the member. The provision of multiple microporous portions allows the fluid delivery device of the present invention to treat multiple sites within the body simultaneously.

In accordance with one aspect of the present invention, a method is provided for manufacturing a radially expandable device for delivery of a fluid to a treatment site within the body. The method includes the step of forming a tube of inelastic, fluoropolymer material through an extrusion and expansion process having selected

process parameters. The tube has a porosity corresponding to the selected process parameters. A radial expansion force is applied to the tube to expand the tube from an initial diameter to a second diameter. The expansion force is then removed. The resultant tube is radially expandable from a reduced diameter to the second diameter upon application of a radial deployment force from a deployment mechanism within the tube. The deployment mechanism can be, for example, a fluid injected into the tube or a radial expansion element inserted into the tube.

The tube can be constructed through an extrusion and expansion process, including the step of creating a billet by blending a mixture of a fluoropolymer and a lubricant and compressing the mixture. The fluoropolymer is preferably PTFE. The billet can then be extruded to form an extruded article. The lubricant is removed and the extruded article is expanded to form a monolithic tube of inelastic, expanded fluoropolymer material. The stretched tube is then heat set to lock in the microstructure of the tube and maintain the tube in the stretched state.

In accordance with a further aspect of the present invention, at least one of the extrusion and expansion process parameters can be varied to form a microporous portion of the wall having a porosity sufficient for the pressurized fluid to permeate through the wall. For example, the lubricant density, the lubricant viscosity, the lubricant molecular weight, the amount of lubricant and/or the longitudinal stretch ratio can be selectively varied to form the microporous portion of the tube. The process parameters can also be varied to produce increased regions of porosity with the microporous region or to form multiple microporous regions.

The extruded article is preferably bilaterally stretched in two opposing directions along the longitudinal axis of the article. Bilaterally stretching the extruded article yields an article that is substantially uniformly stretched over a major portion of its length and has a microstructure of nodes interconnected by fibrils. Bilateral stretching can further result in the formation of a microstructure in which the nodes are oriented substantially perpendicular to the longitudinal axis of the article such that the spaces between the nodes form microchannels extending from the inner to the outer surface of

the wall of the member. The bilateral stretching step can be carried out by displacing the ends of the extruded article either simultaneously or sequentially.

In accordance with another aspect of the present invention, the step of applying a radial expansion force to the tube is carried out by inserting a balloon into the tube and expanding the balloon to apply the radial expansion force to the tube. Preferably, the balloon is constructed from an inelastic material such as, for example, polyethylene terephthalate (PET), nylon, or ePTFE. In a preferred embodiment, the balloon is constructed to be expandable to a predefined size and shape by inflation with a fluid. Radial expansion of the expanded fluoropolymer tube with such an inelastic balloon imparts the predetermined size and shape of the balloon to the expanded fluoropolymer balloon.

In accordance with a further aspect of the present invention, the step of radially expanding the expanded fluoropolymer tube plastically deforms the tube beyond its elastic limit to the second diameter. Plastically deforming the fluoropolymer tube to the second diameter contributes to the expansion device dependably expanding to the second diameter upon application of the radial deployment force.

The step of radially expanding the expanded fluoropolymer tube can also include the steps of positioning the tube within the internal cavity of a mold fixture and radially expanding the balloon within the tube while the tube remains positioned in the internal mold cavity. The internal mold cavity preferably has a size and shape analogous to the predefined size and shape of the balloon. The internal cavity of the mold facilitates concentric radial expansion of the balloon and the fluoropolymer tube.

In accordance with a further aspect of the present invention, the radially expandable fluid delivery of the present invention is particularly suited for treatment of body passages and grafts occluded by disease. The fluid delivery device can be utilized in the manner of a catheter balloon suitable for deployment within a body vessel by a catheter. Exemplary treatment applications of the present application include dilation of stenotic blood vessels in a percutaneous transluminal angioplasty procedure (PCA), removal of thrombi and emboli from obstructed blood vessels, urethra dilation to treat

prostatic enlargement due to benign prostate hyperplasia (BPH) or prostatic cancer, and generally restoring patency to body passages such as blood vessels, the urinary tract, the intestinal tract, the kidney ducts, or other body passages. Exemplary therapeutic agents that can be delivered through the fluid delivery device of the present invention include thrombolytics, antibiotics, antisense oligonucleotides, chemotherapeutics, surfactants, diagnostic agents, steroids, vasodilators, vasoconstrictors, and embolic agents.

Brief Description of the Drawings

These and other features and advantages of the present invention will be more fully understood by reference to the following detailed description in conjunction with the attached drawings in which like reference numerals refer to like elements through the different views. The drawings illustrate principles of the invention and, although not to scale, show relative dimensions.

FIGURE 1 is a side elevational view in cross-section of a radially expandable fluid delivery device according to the teachings of the present invention, illustrating the device in a first, reduced diameter configuration;

FIGURE 2 is a side elevational view in cross-section of the radially expandable fluid delivery device of FIGURE 1, illustrating the device in a second, increased diameter configuration;

FIGURE 3 is a side elevational view of an alternative embodiment of the radially expandable fluid delivery device of the present invention, illustrating the device in the second, increased diameter configuration;

FIGURE 4 is a side elevational view of an alternative embodiment of a radially expandable fluid delivery device of the present invention having multiple axially-spaced microporous portions, illustrating the device in the second, increased diameter configuration;

FIGURE 5 is a cross-sectional view of an alternative embodiment of a radially expandable fluid delivery device of the present invention having an arcuate-shaped

microporous portion, illustrating the device in the second, increased diameter configuration;

FIGURE 6 is a cross-sectional view of an alternative embodiment of a radially expandable fluid delivery device of the present invention having multiple circumferentially-spaced microporous portions, illustrating the device in the second, increased diameter configuration;

FIGURE 7 is a flow chart illustrating the steps of manufacturing a fluid delivery device according to the teachings of the present invention;

FIGURE 8 is a schematic representation of the microstructure of an expanded fluoropolymer tube used during the manufacturing process of the present invention to yield the fluid delivery device of FIGURE 1;

FIGURE 9A is a side elevational view in cross-section of an inelastic balloon positioned within an expanded fluoropolymer tube, illustrating the inelastic balloon in a deflated condition in accordance with a method of manufacturing a fluid delivery device according to the teachings of the present invention;

FIGURE 9B is a side elevational view in cross-section of the inelastic balloon and the expanded fluoropolymer tube of FIGURE 9A, illustrating the inelastic balloon in an inflated condition in accordance with a method of manufacturing a fluid delivery device according to the teachings of the present invention;

FIGURE 9C is a side elevational view in cross-section of the inelastic balloon and the expanded fluoropolymer tube of FIGURE 9A, illustrating the removal of the deflated inelastic balloon from the expanded fluoropolymer tube in accordance with a method of manufacturing a fluid delivery device according to the teachings of the present invention;

FIGURE 10 is a schematic of a system for inflating an inelastic balloon with an expanded fluoropolymer tube in accordance with a method of manufacturing a fluid delivery device according to the teachings of the present invention;

FIGURE 11 is a side elevational view of an inelastic balloon and an expanded fluoropolymer tube positioned within the internal cavity of a mold fixture, illustrating the inelastic balloon in an inflated condition in accordance with a method of manufacturing a fluid delivery device according to the teachings of the present invention;

FIGURE 12 is a side-elevational view in cross-section of a catheter deployed infusion balloon according to the teachings of the present invention, illustrating the infusion balloon expanded within a body vessel;

FIGURE 13 is a flow chart illustrating the steps of an alternative method of manufacturing a fluid delivery device according to the teachings of the present invention;

FIGURE 14A is an electron micrograph of an external section of an ePTFE tube used in the manufacture of the fluid delivery device of the present invention;

FIGURE 14B is an electron micrograph of an external section of a fluid delivery device of the present invention;

FIGURE 14C-14D are electron micrographs of an external section of the neck of the fluid delivery device of FIGURE 14B; and

FIGURE 15 is a side elevational view in cross-section of a multi-layer radially expandable fluid delivery device in accordance with the present invention, illustrating the device in a second, increased diameter configuration.

Detailed Description of the Preferred Embodiments

A radially expandable fluid delivery device 10 having an extensible member 12 constructed of a biocompatible fluoropolymer material is illustrated in FIGURES 1 and 2. The radially expandable fluid delivery device 10 of the present invention is suitable for a wide range of treatment applications. Such applications include use of the fluid delivery device 10 as a catheter balloon for treatment of body passages and grafts such as blood vessels, the urinary tract, the intestinal tract, kidney ducts, natural and synthetic grafts, etc. Specific examples include as a device for the removal of obstructions such as emboli and thrombi from blood vessels, as a dilation device to restore patency to an occluded body passage, as an occlusion device to selectively obstruct a body passage, and as a centering mechanism for transluminal instruments and catheters. In each of these applications, the fluid delivery device 10 can simultaneously deliver a fluid, such as a therapeutic agent, to the body vessel, or the tissue or organs surrounding the body vessel, to effect local treatment with the agent.

The extensible member 12 of the radially expandable fluid delivery device 10 is deployable upon application of an expansion force from a first, reduced diameter configuration, illustrated in FIGURE 1, to a second, increased diameter configuration, illustrated in FIGURE 2. The extensible member 12 of the fluid delivery device 10 of the present invention preferably features a monolithic construction, i.e., the extensible member 12 is a singular, unitary article of generally homogeneous material. The extensible member 12 is manufactured in accordance with the methods of manufacturing of the present invention, an extrusion and expansion process described in detail below, to yield an extensible member 12 characterized by a seamless construction of inelastic, expanded fluoropolymer having a predefined size and shape in the second, increased diameter configuration. The extensible member 12 can be dependably and predictably expanded to the predefined, fixed maximum diameter and to the predefined shape independent of the expansion force used to expand the device.

Referring specifically to FIGURE 2, the extensible member 12 of the fluid delivery device 10 of the present invention is generally tubular in shape when expanded, although other cross sections, such as rectangular, oval, elliptical, or polygonal, can be utilized. The cross-section of the extensible member 12 is continuous and uniform along

the length of the extensible member. However, in alternative embodiments, the cross-section can vary in size and/or shape along the length of the extensible member.

FIGURE 1 illustrates the extensible member 12 relaxed in the first, reduced diameter configuration. The extensible member 12 has a central lumen 13 extending along a longitudinal axis 14 between a first end 16 and second end 18.

A deployment mechanism in the form of an elongated hollow tube 20 is shown positioned within the central lumen 13 to provide a radial deployment or expansion force to the extensible member 12. The tube 20 can be, for example, a catheter constructed from PEBAX tubing available from Elf Atochem of France. The tube 20 is selected to have an outer diameter approximately equal to the diameter of the central lumen 13 of the extensible member 12 in the reduced diameter configuration. The radial deployment force effects radial expansion of the extensible member 12 from the first configuration to the second increased diameter configuration illustrated in FIGURE 2. The first end 16 and the second end 18 are connected in sealing relationship to the outer surface of the hollow tube 20. The first and second ends 16 and 18 can be thermally bonded, bonded by means of an adhesive, or attached by other means suitable for inhibiting fluid leakage from the first and second ends 16 and 18 between the walls of the extensible member 12 and the tube 20.

The hollow tube 20 includes an internal, longitudinal extending lumen 22 and a number of side-holes 24 that provide for fluid communication between the exterior of the tube 20 and the lumen 22. The tube 20 can be coupled to a fluid source (not shown) to selectively provide fluid, such as water, a contrast medium, or saline, to the lumen 13 of the extensible member 12 through the lumen 22 and side-holes 24. The pressure from the fluid provides a radial expansion force on the extensible member 12 to radial expand the extensible member 12 to the second, increased diameter configuration. Because the extensible member 12 is constructed from an inelastic material, uncoupling the tube 20 from the fluid source or otherwise substantially reducing the fluid pressure within the lumen 13 of the extensible member 12, does not generally result in the extensible member 12 returning to the first, reduced diameter configuration. However, the extensible member 12 will collapse under its own weight to a reduced diameter. Application of negative pressure, from, for example, a vacuum source, can be used to

completely deflate the extensible member 12 to the initial reduced diameter configuration.

One skilled in the art will appreciate that the expansion device 10 of the present invention is not limited to use with deployment mechanisms employing a fluid deployment force, such as hollow tube 20. Other known deployment mechanisms can be used to radially deploy the expansion device 10 including, for example, mechanical operated expansion elements, such as mechanically activated members or expansion elements constructed from temperature activated materials such as nitinol.

The extensible member 12 is defined by a wall 30 of biocompatible fluoropolymer material having a thickness extending between an outer surface 32 and an inner surface 34 of the extensible member 12. The inner surface 34 defines the lumen 13 of the extensible body 12. The wall 12 of biocompatible fluoropolymer material is characterized by a microstructure of nodes interconnected by fibrils. FIGURES 1 and 2 provide schematic representations of the microstructure of the extensible member 12. For purposes of description, the microstructure of the extensible member has been exaggerated. Accordingly, while the dimensions of the microstructure are enlarged, the general character of the illustrated microstructure is representative of the microstructure of the extensible member 12.

The extensible member 12 includes at least one microporous portion 40 having a porosity sufficient for the flow of fluid from the lumen 13 through the wall 30, i.e. from inner surface 34 to outer surface 32. The microstructure of the wall 30 within the microporous portion 40 is characterized by a plurality of nodes 36 interconnected by fibrils 38. Preferably, all or substantially all of the nodes 36 within the microporous portion 40 are oriented perpendicular to the inner surface 34 and the outer surface 32 of the extensible member 12 as well as parallel to each other. This preferred orientation of the nodes 36 provides internodal spaces that form pores or micro-channels 42 that extend between the inner surface 34 and the outer surface 32 of the extensible member 12. The micro-channels 42 are sized to permit the flow of fluid between the nodes 36 through the wall 30.

The size of the micro-channels or pores 42 can be selected through the manufacturing process of the present invention, described in detail below. Preferably, the internodal distance of microstructure of the wall within the microporous region, and hence the width of the micro-channels, is approximately $1\mu\text{m}$ to approximately $150\mu\text{m}$. Internodal distances of this magnitude can yield flow rates of approximately 0.01 ml/min to approximately 100 ml/min of fluid through the wall 30 of the extensible member 12.

In a preferred embodiment, the size of the micro-channels or pores 42 within the microporous portion 40 is uniform throughout the microporous portion. In this manner, the flow-rate of fluid through the wall of the microporous portion 40 is also generally uniform. In some applications, however, it may be desirable to have an area of increased or decreased porosity within the microporous portion such that the flow-rate can be tailored to the particular geometry of the site being treated. For example, if a particular region at the treatment site requires increased concentrations of the therapeutic agent, the flow rate at the corresponding section of the microporous portion can be increased to thereby increase the volume of therapeutic agent be delivered to the particular region. Additionally, it is often desirable to reduce the volume of therapeutic agent delivered to the periphery of the treatment site to minimize damage to healthy tissue adjacent the site. The pore size within the microporous region thus can be varied axially or circumferentially, or both, to form such areas of increased or decreased porosity.

The terms "axial" and "axially" as used herein refers to a direction generally parallel to the longitudinal axis of the extensible member 12. The terms "circumferential" and "circumferentially" as used herein refers to a direction generally parallel to the circumference of the extensible member 12. The explanation of these terms is not, however, to be construed to limit the extensible member 12 to a circular cross-section. As discussed above, the cross-section can be any of a number shapes. In the case of non-circular cross-sections, the terms "circumferential" and "circumferentially" as used herein to generally refer to a direction parallel to the perimeter of the extensible member.

The axial length, as well as the axial position, of the microporous portion 40 of the extensible member 12 can be varied to accommodate specific treatment applications. As illustrated in FIGURE 2, for example, the microporous portion 40 can extend along the entire inflatable length of the extensible member 12. In particular, the microporous portion 40 includes a section 40b that is oriented parallel to the longitudinal axis 14 of the extensible member 12 as well as two spaced apart tapered sections 40b and 40c. In the embodiment illustrated in FIGURE 2, thus, the microporous portions 40a, 40b, and 40c extend along the entire length of the extensible member 12, absent the first and second ends 16 and 18, which are sealed to the hollow tube 20.

The microporous portion 40 need not extend the entire inflatable length of the extensible member 12 but instead can include only sections of the length of the extensible member 12. For example, as illustrated in FIGURE 3, the microporous portion can include only section 40b, the section oriented parallel to the longitudinal axis 14 of the extensible member 12. Tapered section 44 and 46 adjacent the microporous portion 40b can be substantially impermeable to the fluid within the extensible member 12. The tapered sections 44 and 46 can be formed with the same microstructure as the microporous portions 40b, i.e. nodes of the same size and orientation, and can be sealed with a coating provided on the inner surface 34 or the outer surface 32 to inhibit fluid flow through the sections 44 and 46. Alternatively, the microstructure of the tapered sections 44 and 46 can have an impermeable, non-porous structure. For example, the nodes forming the microstructure of the tapered sections 44 and 46 can be spaced apart or oriented to inhibit or prevent fluid from passing therethrough.

Moreover, two or more microporous portions of similar or different axial lengths can be provided on the extensible member 12. For example, the extensible member 12 can be provided with three axially spaced microporous portions 40e, as shown in FIGURE 4. Each of the microporous portions 40e is bordered axially by an impermeable portion 48. The microporous portions 40e provide porous, fluid permeable annular zones that are spaced lengthwise along the extensible member 12. The microporous portions 40e can be equally spaced and of similar size, as illustrated in FIGURE 4, or, in the alternative, can be distinctly sized and spaced. One skilled in the art will appreciate that the number of independent microporous portions is not limited to

three as shown in FIGURE 4, but can include two or more zones as dictated by the length of the extensible member 12 and the desired size of the microporous portions.

Referring to FIGURES 5 and 6, the size and position of the microporous portion can be varied circumferentially as well as axially. For example, the microporous section need not extend about the entire circumference of the extensible member 12. FIGURE 5 illustrates an alternative embodiment in which the microporous portion 40f generally extends about one-half of the circumference of the extensible member to form an arc-shaped section that is permeable to fluid within the extensible member 12. An impermeable arc-shaped section 50 is positioned adjacent the arc-shaped microporous portion 40f. Additionally, two or more microporous portions can be spaced circumferentially about the extensible member 12. FIGURE 6 shows an alternative embodiment including four equally spaced arcuate microporous portions 40g. Arc-shaped impermeable portions 52 are spaced between the microporous portions 40g. As in the case of the embodiments described above, the microporous portions 40g can be equally spaced and of similar size, as illustrated in FIGURE 6, or, in the alternative, can be distinctly sized and spaced. Further, the number of microporous portions described is exemplary only; the number of microporous portions is limited only by the circumference of the extensible member 12 and the desired size of the microporous portions.

The impermeable sections of each of the embodiments described above can be constructed of the same microstructure as the microporous portions adjacent thereto, i.e. nodes having the same size and orientation. The impermeable sections can be made impermeable by sealing the sections with a coating provided on either the inner surface 34 or the outer surface 32, or both, to inhibit or prevent fluid flow through the sections. Alternatively, the microstructure of the impermeable sections can be constructed to have an inherently impermeable, non-porous structure. For example, the nodes forming the microstructure of the impermeable sections can be spaced apart or oriented to inhibit or prevent fluid from passing therethrough.

Various fluoropolymer materials are suitable for use in the present invention. Suitable fluoropolymer materials include, for example, polytetrafluoroethylene (PTFE)

or copolymers of tetrafluoroethylene with other monomers may be used. Such monomers include ethylene, chlorotrifluoroethylene, perfluoroalkoxytetrafluoroethylene, or fluorinated propylenes such as hexafluoropropylene. ePTFE is the preferred material of choice. Accordingly, while the fluid delivery device 10 can be manufactured from various fluoropolymer materials, and the manufacturing methods of the present invention can utilize various fluoropolymer materials, the description set forth herein refers specifically to ePTFE.

A method of manufacturing a fluid delivery device in accordance with the present invention will be described in connection with the flow chart shown in FIGURE 7. The fluid delivery device 10 of the present invention is produced from a tube constructed of expanded fluoropolymer material, which is preferably produced through an extrusion and a longitudinal expansion process. The preferred fluoropolymer material is expanded PTFE (ePTFE), which is a hydrophobic, biocompatible, inelastic material having a low coefficient of friction, although, as discussed above, other inelastic, biocompatible fluoropolymer materials may be used.

To produce the ePTFE tube, a billet comprising a PTFE resin mixed with an organic lubricant is utilized. Various organic lubricants are suitable such as naphtha, ISOPAR-G and ISOPAR-H available from Exxon Corporation. The blended resin is compressed at low pressure to yield a tubular billet of PTFE resin and lubricant, step 210 of FIGURE 7. The tubular billet is then extruded through an extruder, for example a ram extruder, to reduce the cross section of the billet and to yield a tubular extrudate, step 212. The organic lubricant can be removed from the extrudate by drying the extrudate in a heated oven, step 214.

Once the tubular extrudate is produced, the extrudate is expanded by longitudinal stretching, step 216. Preferably, the extrudate is bilaterally stretched. Bilateral stretching is accomplished by displacing both ends of the extrudate, sequentially or simultaneously, away from the center of the extrudate. Bilateral stretching provides a material that is homogeneously stretched over the majority of its length and yields a uniform porosity over the length of the material. After the extrudate has been stretched,

it is heat set to lock in the microstructure of the material, step 218 of FIGURE 7, and to complete the process of the forming the tube 110 of ePTFE.

FIGURE 8 is a schematic representation of the ePTFE tube 110 as formed by the extrusion and expansion process described above. For purposes of description, the microstructure of the tube 110 has been exaggerated. Accordingly, while the dimensions of the microstructure are enlarged, the general character of the illustrated microstructure is representative of the microstructure prevailing within the tube 110.

The microstructure of the ePTFE tube 110 is characterized by nodes 130 interconnected by fibrils 132. The nodes 130 are generally aligned with one another and are generally oriented perpendicular to the longitudinal axis 114 of the tube 110. Substantially all of the nodes 130 extend along a transverse axis 134 from an inner surface 136 to an outer surface 138 of the tube 110. This microstructure of nodes 130 interconnected by fibrils 132 provides a microporous structure having microfibrillar spaces which define generally aligned through-pores or channels 134 extending entirely from the inner wall 136 and the outer wall 138 of the tube 110. The through-pores 134 are perpendicularly oriented (relative to the longitudinal axis 114), internodal spaces that traverse from the inner wall 136 to the outer wall 138. The size and geometry of the through-passages can be altered through the extrusion and expansion process, to yield a microstructure that is impermeable, semi-impermeable, or permeable.

Although it is preferable for the micro-channels of the ePTFE tube 110, and the resultant fluid delivery device 10, to be oriented generally perpendicular to the longitudinal axis of the tube ePTFE 110 or fluid delivery device 10, other orientations of the micro-channels can be utilized. For example, by twisting or rotating the ePTFE tube during the extrusion and/or stretching process, the micro-channels can be oriented at an angle to an axis perpendicular to the longitudinal axis of the tube.

In a preferred embodiment, the ePTFE tube 110, and the resultant fluid delivery device 10, has a fine nodal structure that is uniform throughout the cross section and length of the ePTFE tube. The preferred uniform fine nodal structure provides the fluid delivery device 10 with improved expansion characteristics as the expandable device

dependably and predictably expands to the second diameter. The preferred fine nodal structure is characterized by nodes having a size and mass less than the nodes found in conventional ePTFE grafts, preferably in the range of $25\mu\text{m}$ to $30\mu\text{m}$. Additionally, the spacing between the nodes, referred to as the internodal distance, and the spacing between the fibers, referred to as the interfibril distance, is also preferably less than found in conventional ePTFE grafts, preferably in the range of $1\mu\text{m}$ to $5\mu\text{m}$. Moreover, the internodal distance and the interfibril distance in the preferred embodiment is preferably uniform throughout the length and the cross section of the ePTFE tube. The preferred uniform nodal structure can be created by forming the billet with a uniform lubricant level throughout its cross section and length. Stretching the tubular extrudate at higher stretch rates, for example at rates greater than 1 in/s, yields the preferred fine nodal structure. Preferably, the extrudate is stretched at a rate of approximately 10 in/s or greater.

Continuing to describe the manufacturing method of the present invention and referring to FIGURES 7 and 9A, the ePTFE tube 110, having an initial diameter d, is pulled over a balloon 112 to position the balloon 112 within the lumen 114 of the tube 110, step 220 of FIGURE 7. The balloon 112 is preferably constructed of an inelastic material such as, for example, PET, nylon, or PTFE, such that the balloon 112, when inflated, attains a predetermined size and shape. The balloon 112 can be bonded or otherwise coupled to a rigid catheter or hypo-tube 116 to facilitate placement and removal of the ePTFE tube as described below. The catheter 116 has a central inflation lumen 118 and a plurality of side-holes 120 to provide for the delivery of an inflation fluid to inflate the balloon 112. Prior to placement of the ePTFE tube 110 over the balloon 112, a small amount of negative pressure (vacuum) can be applied to the balloon 112 to reduce the balloon to a minimum deflated profile.

Referring to FIGURE 10, a system 148 for inflating the balloon 112 within the ePTFE tube is illustrated. The balloon 112 and the ePTFE tube 110 are positioned within water heated chamber 150, step 222 of FIGURE 6. The catheter 116 is connected by plastic tubing 152 to a pump 154, such as an ISCO syringe pump, for inflation of the balloon 112 with a fluid. Heated water from a circulating temperature bath 158 is pumped through the chamber 150 by a pump 160 to maintain the water within the

chamber 150 at a desired temperature. The water within the chamber 150 is heated to a temperature between approximately 35°C and approximately 60°C. The preferred temperature of the water within the chamber 150 is 50°C. The constant, elevated temperature provided by the circulating water can contribute to uniform expansion, both circumferentially and longitudinally, of the ePTFE balloon, as well as uniform wall thickness.

Referring to FIGURES 9B and 10, the balloon 112 can be inflated by introduction of pressurized fluid from the pump 154 to the lumen 114 of the ePTFE tube 110. The overlying ePTFE tube 110 expands with the inelastic balloon 122 until both the balloon 112 and the ePTFE tube 110 obtain the predetermined size and shape of the inflated balloon 112, step 224 of FIGURE 7. The inflated balloon 112 thus imparts its predetermined size and shape to the ePTFE tube 110. This radially expansion process is referred to as “blow-molding”. The PTFE tube 110 shown in FIGURE 9B is radially expanded from the initial diameter d (FIGURE 9A) to an increased diameter D .

It is preferable for the ePTFE tube 110 to be plastically deformed by the radial expansion of the inelastic balloon 112, step 226 of FIGURE 7. The terms “plastic deformation” and “plastically deform,” as used herein, is intended to include the radial expansion of the ePTFE tube 110 beyond the elastic limit of the ePTFE material such that the ePTFE material is permanently deformed. Once plastically deformed, the ePTFE material forming the tube 110 becomes substantially inelastic, i.e., the ePTFE tube generally will not, on its own, return to its pre-expansion size and shape.

The ePTFE tube 110 can be removed from the balloon 112 by removing the inflation fluid from the balloon 112 using the pump 154 and sliding the ePTFE tube 110 relative to balloon 112 and catheter 116, i.e. in the direction of arrows A in FIGURE 9C, step 228 of FIGURE 7. The tube 110 can be heat set at a temperature above the sinter point of the material forming the tube, 360°C for ePTFE, to lock in the structure of the tube 110, step 230 of FIGURE 7. The pump 150 can be used to provide a slight vacuum within the balloon 112 to facilitate removal of the ePTFE tube 110.

The ePTFE tube 110 can be attached to a deployment mechanism such as hollow tube 20 described above, step 232 of FIGURE 7. A suitable adhesive can be used to secure the ePTFE tube to the deployment mechanism.

Referring to FIGURE 11, an alternative method of manufacturing a radially expandable device employing a mold 202 is illustrated. The mold 202 includes two interconnected sections 204 and 206 forming an internal mold cavity 208 for receiving the ePTFE tube 110 with the balloon 112 positioned therein. The mold 202 is preferably constructed of a rigid, unyielding material such as a metal or metal alloy. Suitable metals or metal alloys include brass and steel alloys. The internal mold cavity 208 preferably has a size and shape analogous to that of the inflated balloon 112 to ensure that the inflated balloon 112, and the overlying ePTFE tube 110 concentrically expand.

Referring to the flow chart illustrated in FIGURE 13, a further alternative method of manufacturing a fluid delivery device according to the teachings of the present invention will be described. A tube constructed of ePTFE is formed in accordance with the methods described above, step 410. A tube formed of an extruded inelastic material such as PET is used in place of balloon 112 to radially expand the ePTFE tube. The extruded tube is positioned within the ePTFE tube 110, step 412. The extruded tube is then sealed at one end and attached to an inflation system at the other end, step 414. The extruded tube can then be inflated by an inflation medium to radially expand the ePTFE tube, step 416. The extruded tube and ePTFE tube are preferably heated to the glass transition temperature of the extruded tube, approximately 80°C - 100°C for PET, as the extruded tube is inflated within the ePTFE tube. It is preferable to limit the temperature of the extruded tube to a temperature less than or equal to the glass transition temperature of the material forming the extruded tube to facilitate removal of the extruded tube from the ePTFE tube. Heating the extruded tube to a temperature above the glass transition temperature will cause the extruded tube to heat set in an expanded configuration, which makes removing the extruded tube from the ePTFE tube difficult.

After the extruded tube and ePTFE tube are expanded to desired size and shape, the extruded tube is deflated and removed from the ePTFE tube, step 418. The ePTFE tube is then heat set to lock in the structure of the ePTFE tube, step 420.

A mold, such as mold 202, can be employed during radial expansion of the ePTFE tube using the PET tube. The mold is preferably heated within the hot water chamber of an inflation system, such as inflation system 148 illustrated in FIGURE 10, or by other means such as a hot oil bath or through a steam, hot air, electric, radio frequency or infra red heat source. The mold can be constructed of a material having good heat transfer characteristics, such as metal or metal alloy, for example brass. The mold includes a mold cavity having a size and shape analogous to the desired size and shape of the fluid delivery device 10 in the second diameter configuration.

The resultant radially expanded ePTFE tube 110, produced in accordance with the above described methods, provides a radially expandable fluid delivery device, such as the fluid delivery device 10 illustrated in FIGURES 1 and 2 and described above, that is radially expandable from a relaxed, collapsed diameter to the second, increased diameter D upon application of a radial deployment force from a deployment mechanism within the tube 110. Moreover, the microstructure of the radially expanded ePTFE tube 110 can be manufactured through the process of the present invention to have a porosity sufficient to permit fluid to flow therethrough. In particular, the microstructure of the resultant fluid delivery device is analogous to the microstructure of the ePTFE tube 110, i.e. nodes interconnected by fibrils, the space between the nodes defining micro-channels through the wall of the device.

One feature of the manufacturing processes of the present invention is that the microporous structure of the ePTFE tube 110 forming the fluid delivery device 10 can be manipulated by varying the extrusion and expansion process parameters to produce different porosity characteristics. For example, the longitudinal stretch ratio of the ePTFE tube 110, i.e., the ratio of final stretched length of the tube to the initial length, and the diametric stretch ratio of the ePTFE tube 110, i.e., the ratio of the final diameter, after longitudinal stretching, and the initial diameter, and the stretch rate can be varied to yield fluid recovery devices having different porosity. Applicants determined that larger longitudinal stretch ratios, in the order of 2:1 to 3:1, can result in a ePTFE tube having a microstructure characterized by increased internodal distances and interstitial

space, i.e., the micro-channels within the microstructure of the ePTFE tube are increase in sized. Suitable longitudinal stretch ratios can be from 1.1:1 to 10:1.

Fluid delivery devices formed from ePTFE tubes having larger stretch ratios require minimal fluid pressure within the device to achieve the desired flow rate of fluid through the walls of the device. Such fluid delivery devices will consequently provide little radially-outward dilation force, which can be advantageous for some applications such as delivering therapeutic or diagnostic agents to healthy tissue. Conversely, ePTFE tubes having smaller stretch ratios result in fluid delivery devices that are less porous, as the internodal distances are reduced, and, thus, generally require increased fluid pressure to deliver the fluid. Such fluid delivery devices consequently provide increased radially outward dilation force, which can be advantageous for treatment applications such as reducing arterial lesions with pressure. Accordingly, the porosity of the ePTFE tube, and hence the porosity of the resultant fluid delivery device, is dependent on the stretch ratios of the expansion process. By manipulating the stretch ratios of the ePTFE tube, i.e. increasing or decreasing the stretch ratios, the porosity of the fluid delivery device can be tailored to the specific treatment application.

The porosity of the ePTFE tube, and the subsequent fluid delivery device, can also depend on the density, the viscosity, the molecular weight, and the amount of lubricant used to form the billet used in the extrusion and expansion process. Increasing the amount by weight of lubricant or increasing the density or molecular weight of the lubricant, results in an extrudate having increased internodal distances and interstitial spaces prior to the step of expansion. Once stretched, the resultant ePTFE tube will reflect the increased porosity.

The process described above can be used to produce fluid delivery devices having a uniform porosity though out the length of the device. To produce discrete microporous portions within the fluid delivery devices a number of different processes can be employed. For example, a coating can be applied at select locations to the inner and/or outer surfaces of the fluid delivery device to produce impermeable sections within the device. The coating preferable seals the microchannels within the microstructure of the device to inhibit or prevent fluid from passing therethrough.

Alternatively, the porosity of the ePTFE tube can be selectively reduced subsequent to the step of expansion by applying heat to the select sections of the tube to return the sections to the pre-stretched porosity. The selectively heated sections will thus yield sections of reduced porosity. By controlling the amount of heat applied, the sections of reduced porosity can be made semi-permeable or impermeable to fluid.

In addition to selecting and varying the porosity of the fluid recovery device through the manufacturing process of the present invention, the parameters of the manufacturing process can be varied to produce an ePTFE tube having distinct expansion characteristics. The size and shape of the fluid recovery device of the present invention can also be varied. These processes are described in detail in Applicants' co-pending U.S. Patent Application Serial Number _____ (Attorney Docket No. ATA-132), filed on _____, which is incorporated herein by reference.

FIGURE 12 illustrates an exemplary embodiment of the fluid delivery device of the present invention in which the fluid delivery device 10 of FIGURE 1 is utilized as a catheter deployed dilation and diffusion balloon 300 for the treatment of a blood vessel 310 partially occluded by plaque deposits 312 adhered to the walls 314 of the blood vessel. This procedure is generally referred to as a Percutaneous Transluminal Angioplasty (PTA) procedure. The balloon 300 can be manufactured in accordance with the methods of the present invention and is shown in the expanded configuration. The ends 302 of the dilation balloon 300 are bonded to a catheter tube 320, which is used to provide an inflation fluid to the balloon 300 to effect expansion of the balloon 300 to a predefined and fixed maximum diameter. A therapeutic agent, such as antisense oligonucleotides (AS-ODNs), can be delivered through the walls of the balloon with the inflation fluid. The AS-ODNs are delivered locally to the walls of the body vessel to suppress restenosis of the body vessel subsequent to the PTA procedure.

A variety of therapeutic agents can be delivered with the fluid delivery device of the present invention. Exemplary therapeutic agents include: thrombolytics, antibiotics, chemotherapeutics, surfactants, diagnostic agents, steroids, hot saline, vasodilators, vasoconstrictors, and embolic agents. The localized delivery of thrombolytics, such as

heparin, and urokinase, directly to the surface of thrombosed grafts or native body vessels can inhibit the-clotting of the grafts or native body vessels. The fluid delivery device of the present invention thus can be used as thrombolectomy balloon catheter to remove obstructions from grafts or native body vessels while concomitantly delivering thrombolytics to the walls of the graft or native body vessel.

The fluid delivery device of the present invention can further be used for the localized delivery of high concentrations of antibiotics to treatment sites such as the ear canal, the throat, and the upper respiratory passages. Anti-cancer agents such as chemotherapeutics delivered using the fluid delivery device of the present invention can increase the effectiveness and negate the systemic side effects of the anti-cancer agents. Exemplary forms of cancer targeted for this application can include: rectal, esophageal, and lung cancer. Surfactants can be delivered directly to the lungs using the fluid delivery device of the present invention to treat cystic fibrosis or hyaline membrane disease. Diagnostic agents can be delivered during angiography procedures through the fluid delivery device of the present invention to improve the visibility of contrast agents delivered locally to the treatment site. The local delivery of steroids, such as anabolic steroids, using the fluid delivery device of the present invention can increase the effectiveness, e.g., promote muscle recovery, and negate systemic side effects such as lung and adrenal gland vantage.

The fluid delivery device of the present invention can also be provided with hydrophilic or hydrophobic coatings dependant on the particular treatment applications. For example, fluid delivery devices constructed of ePTFE, a naturally hydrophobic material, can be coated with a hydrophilic coating to provide the fluid delivery device with a hydrophilic outer surface. A suitable hydrophilic coating is PHOTOLINK available from Surmodics of Eden Prairie, MN.

In an alternative embodiment illustrated in FIGURE 15, the fluid delivery device of the present invention can be provided with multiple layers. The multi-layer fluid delivery device 500 includes a first layer 502 of biocompatible material, such as ePTFE, and a second layer 504 of biocompatible material that overlies the first layer 502. The second layer 504 can be constructed from the same or a different biocompatible material

than the first layer 502. As shown in FIGURE 15, the first layer 502 and the second layer 504 are preferably coextensive, however, the second layer 504 need not extend the entire length of the first layer 502. Likewise, the first layer 502 may be smaller in length than the second layer 504.

The first layer 502 and the second layer 504 can each be formed from a separate ePTFE tube. The ePTFE tubes can be constructed in accordance with the manufacturing methods of the present invention such that each tube is characterized by a microstructure of nodes interconnected by fibrils. Preferably the nodes are oriented generally perpendicular to the longitudinal axis. The two ePTFE tubes can then be coaxially disposed and heated to bond the two tubes together. The bonded tubes can be radially expanded by a balloon in accordance with the above manufacturing methods of the present invention. By producing the ePTFE tubes forming the first and second layers using different process parameters, e.g. different stretch ratios or stretch rates, the distance between the nodes can varied between the ePTFE tubes. For example, the internodal distances of the microstructure of the first layer 502 can be generally greater than the internodal distances of the microstructure of the second layer 504. In this manner, the porosity of the first layer 502 and the porosity of the second layer 504 can be different.

Although the multi-layer fluid delivery device 500 illustrated in FIGURE 15 includes two layers, additional layers can be provided. Additional layers can be formed from further ePTFE tubes or through other methods, such as by wrapping ePTFE film about the first layer and/or second layer.

Example 1

An exemplary fluid delivery device was constructed according to the manufacturing processes of the present invention by employing .068" (ID)/.088" (OD) ePTFE tubing. The longitudinal stretch ratio of the ePTFE tube was 1.5:1, at a stretch rate of 10 inches per second. An electron micrograph of an exterior section of a sample ePTFE tube, after stretching, is shown in FIGURE 14A. FIGURE 14A illustrates the microstructure of nodes interconnected by fibrils of the ePTFE tubing and, in particular, the orientation of the nodes generally perpendicular to the longitudinal axis of the tubing

and the internodal through-pores. An 8 mm x 8 cm PET balloon was employed to radially expand the ePTFE tubing. The PET balloon was attached to a vacuum source and a slight vacuum was placed on the PET balloon, about -5 to -10 psi. The ePTFE tubing was then positioned over the deflated PET balloon. The PET balloon and the ePTFE tubing were then connected to a hypo-tube and placed into a water heated chamber. Saline was injected into the PET balloon at a constant flow rate of about 10-15 ml/min. When the pressure within the balloon reached 70-80% of the rated balloon pressure, about 12-15 atm for the PET balloon employed, the flow rate was decreased to 2 ml/min. The balloon was then brought to its rated balloon pressure. The water was then removed from the PET balloon using the pump until a slight vacuum existed within the PET balloon (-5 to -10 psi). The hypo-tube was then removed from the chamber and the ePTFE tube was withdrawn from the balloon. The proximal I.D. of the resultant ePTFE tube was approximately 2/3 Fr larger than the distal I.D.

The resultant ePTFE balloon was then allowed to completely dry. The ePTFE balloon was cut to a desired length and the proximal tail of the ePTFE balloon was dipped into Loctite 7701 Prism Primer, available from Loctite, Corp. of Rocky Hill, CN. The distal tail of the ePTFE balloon was then dipped into the primer. The primer was allowed to evaporate for at least two minutes. The ePTFE balloon was then placed on a 5 Fr- 4 Fr tipped catheter by pulling the proximal end of the ePTFE balloon onto the 5 Fr end of the catheter body until the distal (4 Fr) end is about 0.1" from the tip of the catheter. The location of the proximal tail of the ePTFE balloon was then marked on the catheter and the ePTFE balloon was removed from the catheter. Loctite 4011 adhesive was then applied to the catheter shaft at a location slightly distal to the marked position. The ePTFE balloon was then slid back onto the catheter shaft until the proximal end was aligned with the mark. The adhesive was allowed to dry for one minute. A small volume of Loctite 4011 adhesive was dispensed onto the distal end of the catheter shaft adjacent to the distal end of the ePTFE balloon. This adhesive was drawn into the gap between the catheter and the balloon by capillary forces. The adhesive was then allowed to dry for at 24 hours.

An electron micrograph of an exterior section of a sample ePTFE balloon is shown in FIGURES 14B-14D. FIGURE 14B illustrates the microstructure of nodes

interconnected by fibrils of the body of the ePTFE balloon. FIGURES 14C and 14D are cross-sections of the neck of the ePTFE balloon at varying magnifications. FIGURES 14B-14D illustrate the internodal through-pores or channels of the ePTFE balloon as defined by the microfibrillar spaces between the nodes. The through-pores are oriented generally perpendicular to the longitudinal axis of the ePTFE balloon and provide fluid pathways between the inner surface and the outer surface of the ePTFE balloon.

Example 2

Three ePTFE synthetic grafts were treated using an ePTFE diffusion balloon constructed in accordance with the method of Example 1 to determine the permeability of a contrast agent into the grafts. The diffusion balloon employed was 8 cm in length, had an OD of 6 mm and was constructed from an 0.088" (OD)/.068" (ID) ePTFE tube having a stretch ratio of 1.5:1. Each of the grafts treated was an Atrium Hybrid PTFE graft, model no. 01200670, available from Atrium Medical of Hudson, NH. The grafts had a 6mm inner diameter and a wall thickness of .025 inches. In each case, the balloon was inserted into a graft and inflated by infusing a contrast agent. The balloon was inflated to 1 atm. by the infused fluid. The balloon was then removed from the graft and the graft was flushed with water delivered at 500 ml/min. The contrast agent used was Hypaque-76 available from Mycomed, Inc. Table 1 summarizes each procedure.

Table 1

Graft Sample	Duration of Balloon Infusion	Balloon Infusion Fluid	Graft Flushing Duration
1	15 seconds	Saline & Contrast Agent	5 minutes
2	15 seconds	Saline & Contrast Agent	30 seconds
3 (Control)	15 seconds	Saline	No Flushing

X-rays were taken of each of the grafts samples to determine if the contrast agent was present in the grafts post infusion and perfusion (flushing). Table 2 summarizes the results of the X-rays for each graft.

Table 2

Graft Sample	Presence of Contrast Agent
1	Yes
2	Yes
3	No

Contrast agent was found in the walls of the both ePTFE graft samples infused with contrast agent by the diffusion balloon of the present invention, but not in the control sample. In graft samples 1 and 2, the contrast agent was found to have permeated through the entire wall of the graft. Flushing the grafts with water post infusion was determined to have no effect on the presence and concentration of the delivered contrast agent.

Example 3

The permeability of several ePTFE fluid delivery devices constructed in accordance with the manufacturing processes of the present invention was evaluated and compared with the permeability of selected synthetic grafts. Each of the fluid delivery devices was constructed from an extruded and expanded ePTFE tube as set forth in Table 3.

Table 3

Fluid Delivery Device Sample	Stretch Ratio of ePTFE tube	Stretch Rate of ePTFE tube (in/s)	Wall Thickness of Fluid Delivery Device (in)	Surface Area of Fluid Delivery Device (in ²)
1	1.5:1	20	0.0068	0.456
2	1.75:1	10	0.0055	0.469
3	3:1	10	0.005	0.469
4	5:1	10	0.003	0.503
5	1.25:1	10	0.0075	0.399
6	1.5:1	0.5	0.0055	0.399
7	1.5:1	10	0.005	0.399
8	1.5:1	10	0.005	0.29

The synthetic grafts analyzed were standard and thin wall grafts available from Atrium Medical Corporation and W. L. Gore & Associates, Inc. Information regarding the grafts is set forth in Table 4

Table 4

Graft sample	Type	Wall Thickness (in)	Surface Area (in ²)
A	Atrium 6mm std	0.025	0.964
B	Atrium 6mm thin	0.022	0.963
C	Gore 7mm thin	0.016	1.143
D	Gore 6 mm std	0.024	0.963
E	Gore 4mm	0.025	0.59
F	Atrium 4mm	0.02	0.49

The fluid delivery devices and the synthetic grafts were infused with a fluid to determine the permeability of the samples. The permeability of each of the samples is reflected by the hydrodynamic resistance and the hydraulic conductivity data set forth in Table 5.

Table 5

Sample	Hydrodynamic resistance (psi*min*mL ⁻¹)	Hydraulic Conductivity (cm ⁴ / (dyne* s)* 10 ¹²)
1	21.2	67
2	7.18	155
3	2.76	368
4	2.81	202
5	13.4	134
6	1.59	825
7	1.5	795
8	1.7	966
A	2.394	1031
B	1.03	2112
C	0.711	1874
D	0.623	3808
E	1.5	2673
F	1.2	3207

Hydraulic conductivity was determined using Darcy's Law for describing steady flow through a porous media. Darcy's law is defined in Equation 1 as

$$Q/A = K(\Delta P/\Delta X), \quad (\text{Eq. 1})$$

where Q is flow rate, A is cross sectional area for flow, i.e. the surface area of the sample, P is pressure, X is wall thickness, and K is the hydraulic conductivity.

Applicants determined that the permeability of a fluid delivery device relative to the permeability of the vessel being treated is an important consideration in establishing effective fluid delivery into the walls of the vessel. In particular, for a given fluid flow rate and pressure, a greater volume of fluid will penetrate the walls of a vessel being treated if the permeability of the vessel is greater than the permeability of the fluid delivery device. Accordingly, it is desirable for the permeability of the fluid delivery device to be less than the permeability of the vessel being treated. The permeability of

the fluid delivery device can be tailored to be less than the vessel being treated by varying the process parameters of the manufacturing processes described above. The process parameters include lubricant density, lubricant viscosity, lubricant molecular weight, longitudinal stretch ratio, and stretch rate.

The permeability data set forth in Table 5 illustrates that the permeability, when measured in terms of the hydraulic conductivity, for each of the fluid delivery devices tested was less than the permeability of each of the synthetic grafts tested. This indicates that the Applicants' fluid delivery device may be particularly effective for delivering fluid to the walls of synthetic grafts.

Applicants have determined that it is desirable for the hydraulic conductivity of the fluid delivery device to be less than $1000 \text{ (cm}^4 / (\text{dyne} \cdot \text{s}) \cdot 10^{12})$ for treatment of synthetic grafts. Preferably, the fluid delivery device has a hydraulic conductivity of less than $500 \text{ (cm}^4 / (\text{dyne} \cdot \text{s}) \cdot 10^{12})$. For treatment of natural body vessels and grafts, it is preferable for the hydraulic conductivity of the fluid delivery device to be less than $100 \text{ (cm}^4 / (\text{dyne} \cdot \text{s}) \cdot 10^{12})$.

It will thus be seen that the invention efficiently attains the objects made apparent from the preceding description. Since certain changes may be made in the above constructions without departing from the scope of the invention, it is intended that all matter contained in the above description or shown in the accompanying drawings be interpreted as illustrative and not in a limiting sense.

It is also to be understood that the following claims are to cover all generic and specific features of the invention described herein, and all statements of the scope of the invention which, as a matter of language, might be said to fall therebetween.

Having described the invention, what is claimed as new and desired to be secured by Letters Patent is:

1. A radially expandable fluid delivery device comprising:
a member constructed of a biocompatible material, the member having a longitudinal axis and a wall having a thickness extending between an inner and an outer surface, the wall having a microstructure of nodes interconnected by fibrils, the member being deployable from a first, reduced diameter configuration to a second, increased diameter configuration,
wherein the wall of the member includes at least one microporous portion having a porosity sufficient for a fluid to permeate through the wall, spaces between the nodes substantially controlling the permeation of fluid through the wall.
2. The fluid delivery device of claim 1, wherein the biocompatible material is ePTFE.
3. The fluid delivery device of claim 1, wherein the member has a hydrophillic exterior surface.
4. The fluid delivery device of claim 1, wherein the member has a hydrophobic exterior surface.
5. The fluid delivery device of claim 1, wherein the nodes within the microporous portion are separated by an internodal distance, the internodal distance being approximately $1\mu\text{m}$ - $150\mu\text{m}$.
6. The fluid delivery device of claim 1, wherein substantially all of the nodes within the microporous portion are oriented such that spaces between the nodes form micro-channels extending from the inner surface to the outer surface of the wall.
7. The fluid delivery device of claim 1, wherein the nodes within the microporous portion are oriented substantially perpendicular to the longitudinal axis of the member.
8. The fluid delivery device of claim 1, wherein the micro-channels within the microporous portion of the wall are sized to permit the fluid to pass from the inner surface to the outer surface of the wall.

9. The fluid delivery device of claim 8, wherein the size of the micro-channels varies longitudinally.
10. The fluid delivery device of claim 8, wherein the size of the micro-channels varies circumferentially.
11. The fluid delivery device of claim 1, wherein the member deploys to the second configuration upon application of a fluid having a pressure of approximately 1 psi to 250 psi.
12. The fluid delivery device of claim 1, wherein the microporous portion of the wall has a porosity sufficient to allow fluid to pass therethrough at a flow rate of approximately 0.01 ml/min to 100 ml/min.
13. The fluid delivery device of claim 1, wherein the member has a unitary construction of generally homogenous material.
14. The fluid delivery device of claim 1, wherein the fluid includes a medicinal agent.
15. The fluid delivery device of claim 14, wherein the medicinal agent is selected from the group consisting of thrombolytics, antibiotics, antisense oligonucleotides, chemotherapeutics, surfactants, diagnostic agents, steroids, vasodilators, vasoconstrictors, and embolic agents.
16. The fluid delivery device of claim 1, wherein the microporous portion of the wall borders a second portion of the wall that is generally impermeable to the pressurized fluid.
17. The fluid delivery device of claim 1, wherein the wall further includes a second microporous portion having a porosity sufficient for the fluid to permeate through the wall.

18. The fluid delivery device of claim 17, wherein an impermeable portion of the wall is interposed between the microporous portion and the second microporous portion of the wall.
19. The fluid delivery device of claim 17, wherein the second microporous portion is spaced longitudinally from the microporous portion.
20. The fluid delivery device of claim 17, wherein the second microporous portion is spaced circumferentially from the microporous portion.
21. The fluid delivery device of claim 1, wherein the microporous portion has a hydraulic conductivity less than $1000 \text{ (cm}^4/\text{(dyne} \cdot \text{s))} \cdot 10^{12}$.
22. The fluid delivery device of claim 21, wherein the hydraulic conductivity is less than $500 \text{ (cm}^4/\text{(dyne} \cdot \text{s))} \cdot 10^{12}$.
23. The fluid delivery device of claim 21, wherein the hydraulic conductivity is less than $100 \text{ (cm}^4/\text{(dyne} \cdot \text{s))} \cdot 10^{12}$.
24. The fluid delivery device of claim 1, wherein the fluid delivery device is a medical treatment device for treating a body vessel, the microporous portion has a hydraulic conductivity less than the hydraulic conductivity of the body vessel.
25. An expandable drug delivery device comprising:
a member constructed of a biocompatible fluoropolymer material, the member having a longitudinal axis and a wall having a thickness extending between an inner and an outer surface, the wall having a microstructure of nodes interconnected by fibrils, the member being deployable from a first, reduced diameter configuration to a second, increased diameter configuration upon application of an expansion force to the lumen, at least a portion of the wall having nodes oriented such that spaces between the nodes form generally aligned micro-channels oriented and extending from the inner surface to

the outer surface of the wall, the micro-channels being sized to permit fluid including a therapeutic agent to permeate from the inner surface to the outer surface of the wall.

26. A radially expandable fluid delivery device comprising:

a member constructed of a biocompatible fluoropolymer material, the member having a longitudinal axis and a wall having a thickness extending between an inner and an outer surface, the wall having a microstructure of nodes interconnected by fibrils, the member being deployable from a first, reduced diameter configuration to a second, increased diameter configuration upon application of an expansion force,

wherein the wall of the member includes a first microporous portion having a porosity sufficient for a fluid to permeate through the wall and a second microporous portion spaced apart from the first microporous portion and having a porosity sufficient for a fluid to permeate through the wall.

27. A radially expandable fluid delivery device comprising:

a member constructed of a biocompatible fluoropolymer material, the tubular member having a longitudinal axis and a wall having a thickness extending between an inner and an outer surface, the wall having a microstructure of nodes interconnected by fibrils, the member being deployable from a first, reduced diameter configuration to a second, increased diameter configuration upon application of an expansion force, the wall including a microporous portion having nodes oriented such that spaces between the nodes form micro-channels extending from the inner surface to the outer surface of the wall, the micro-channels being sized to permit a fluid to permeate from the inner surface to the outer surface of the wall,

wherein the size of the micro-channels varies circumferentially about the tubular member to provide regions of greater porosity within the microporous portion.

28. A method of manufacturing a radially expandable fluid delivery device, the method comprising the steps of:

forming a tube of biocompatible fluoropolymer material having a microstructure of nodes interconnected by fibrils through an extrusion and expansion process having selected process parameters, the tube having a porosity corresponding to the selected process parameters, the tube having a longitudinal axis and a wall having a radial

thickness transverse to the longitudinal axis and extending between an inner and an outer surface,

applying a radial expansion force to the tube to expand the tube from the initial diameter to a second diameter, and

removing the expansion force,

wherein the tube is radially expandable from a reduced diameter to the second diameter upon introduction of a pressurized fluid to the lumen of the tube.

29. The method of claim 28, wherein the step of forming the monolithic tube comprises the steps of:

creating a billet by blending a mixture of a fluoropolymer and a lubricant and compressing the mixture,

extruding the billet to form an extruded article having a longitudinal axis,

removing the lubricant from the extruded article,

expanding the extruded article to form the tube of biocompatible fluoropolymer material having a microporous structure, and

heat setting the tube.

30. The method of claim 29, further comprising

varying at least one of the predetermined process parameters to form at least one microporous portion of the wall having a porosity sufficient for the pressurized fluid to permeate through the wall.

31. The method of claim 30, wherein the at least one process parameters is selected from the group consisting of lubricant density, lubricant viscosity, lubricant molecular weight, longitudinal stretch ratio and stretch rate.

32. The method of claim 29, wherein the step of expanding the extruded article further comprises

bilaterally stretching the extruded article in two opposing directions along the longitudinal axis to yield an article which is substantially uniformly stretched over a major portion of its length.

33. The method of claim 28, wherein the step of applying a radial expansion force includes
- inserting a balloon into the tube, and
 - inflating the balloon to apply the radial expansion force to the tube.
34. The method of claim 33, wherein the balloon is expanded by inflation with a fluid.
35. The method of claim 33, wherein the balloon is constructed of an inelastic material.
36. The method of claim 33, further comprising
- providing a mold having an internal cavity,
 - positioning the tube within the internal cavity, and
 - inflating the balloon within the tube while the tube remains positioned in the internal cavity.
37. The method of claim 36, wherein the internal cavity has a size and shape analogous to the predefined size and shape of the balloon.
38. The method of claim 36, wherein the step of radially expanding the tube plastically deforms the tube beyond its elastic limit.
39. The method of claim 28, wherein the step of applying a radial expansion force includes
- inserting a second tube of extruded material into the tube, and
 - expanding the second tube to apply the radial expansion force to the tube.
40. The method of claim 39, wherein the tube and the second tube are heated to the glass transition temperature of the extruded material during the step of radial expansion.
41. The method of claim 39, further comprising
- providing a mold having an internal cavity,

positioning the tube and the second tube within the internal cavity, and radially expanding the tube within the internal cavity.

42. The method of claim 41, further comprising
heating the tube and the second tube to the glass transition temperature of the extruded material during the step of radially expanding the tube within the internal cavity of the mold.
43. The method of claim 28, further comprising
heat setting the tube after the step of applying a radial expansion force to the tube.
44. A medical treatment device comprising:
a catheter having an elongated hollow tube defining an inflation lumen extending from a proximal end to a distal end, and
a balloon constructed of a biocompatible fluoropolymer material and attached to the distal end of the tube, the balloon having a wall having a thickness extending between an inner and an outer surface and a lumen in fluid communication with the inflation lumen of the catheter, the wall having a microstructure of nodes interconnected by fibrils, the balloon being deployable from a first, reduced diameter configuration to a second, increased diameter configuration,
wherein the wall of the balloon includes at least one microporous portion having a porosity sufficient for a fluid to permeate through the wall, substantially all of the nodes within the microporous portion being oriented substantially perpendicular to the longitudinal axis of the balloon.
45. A radially expandable fluid delivery device having a longitudinal axis and a wall transverse to the longitudinal axis, the fluid delivery device comprising:
a first layer of biocompatible material having a microstructure of nodes interconnected by fibrils, and
a second layer of biocompatible material having a microstructure of nodes interconnected by fibrils, the second layer overlying the first layer, the wall of the fluid delivery device extending between an inner surface of the first layer and an outer surface

of the second layer, the fluid delivery device being deployable from a first, reduced diameter configuration to a second, increased diameter configuration,

wherein the wall of the fluid delivery device includes at least one microporous portion having a porosity sufficient for a fluid to permeate through the wall, substantially all of the nodes within the microporous portion being oriented such that spaces between the nodes form generally aligned micro-channels oriented and extending from the inner surface of the first layer to the outer surface of the second layer, the micro-channels being sized to permit fluid to permeate from the inner surface of the first layer to the outer surface of the second layer.

46. The fluid delivery device of claim 45, wherein substantially all of the nodes within the microporous portion being are substantially perpendicular to the longitudinal axis of the member.

47. The fluid delivery device of claim 45, wherein the micro-channels within the first layer are sized differently than the micro-channels within the second layer.

48. The fluid delivery device of claim 45, wherein the node in the first layer are separated by a first internodal distance and the nodes in second layer are separated by a second internodal distance, wherein the first internodal distance is different from the second internodal distance.

49. The fluid delivery device of claim 45, wherein the biocompatible material of the first layer is different than the biocompatible material of the second layer.

50. A radially expandable fluid delivery device comprising:
a member constructed of a biocompatible material, the member having a longitudinal axis and a wall having a microstructure of nodes interconnected by fibrils, the member being deployable from a first, reduced diameter configuration to a second, increased diameter configuration,
wherein the wall of the member includes at least one microporous portion having a porosity sufficient for a fluid to permeate through the wall, the microporous portion having a hydraulic conductivity less than $1000 \text{ (cm}^4/(\text{dyne} \cdot \text{s}) \cdot 10^{12})$.

51. The fluid delivery device of claim 50, wherein the hydraulic conductivity is less than $500 \text{ (cm}^4/(\text{dyne} \cdot \text{s}) \cdot 10^{12})$.

52. The fluid delivery device of claim 50, wherein the hydraulic conductivity is less than $100 \text{ (cm}^4/(\text{dyne} \cdot \text{s}) \cdot 10^{12})$.

Abstract of the Disclosure

A radially expandable fluid delivery device for delivering a fluid to a treatment site within the body is disclosed. The fluid delivery device is constructed of a microporous, biocompatible fluoropolymer material having a microstructure that can provide a controlled, uniform, low-velocity fluid distribution through the walls of the fluid delivery device to effectively deliver fluid to the treatment site without damaging tissue proximate the walls of the device. The fluid delivery device includes a tubular member defined by a wall having a thickness transverse to the longitudinal axis of the tubular member and extending between an inner and an outer surface. The wall is characterized by a microstructure of nodes interconnected by fibrils. The tubular member is deployable from a first, reduced diameter configuration to a second, increased diameter configuration upon the introduction of a pressurized fluid to the lumen. The tubular member includes at least one microporous portion having a porosity sufficient for the pressurized fluid to permeate through the wall. Substantially all of the nodes within the microporous portion are oriented such that spaces between the nodes form micro-channels extending from the inner surface to the outer surface of the wall.

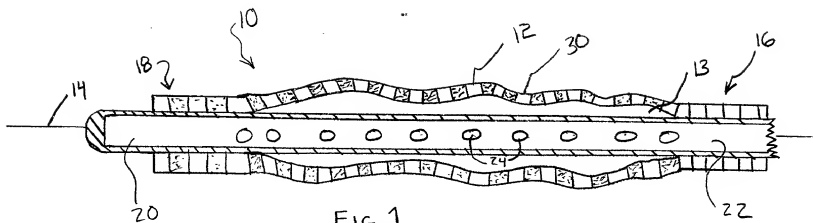


FIG. 1

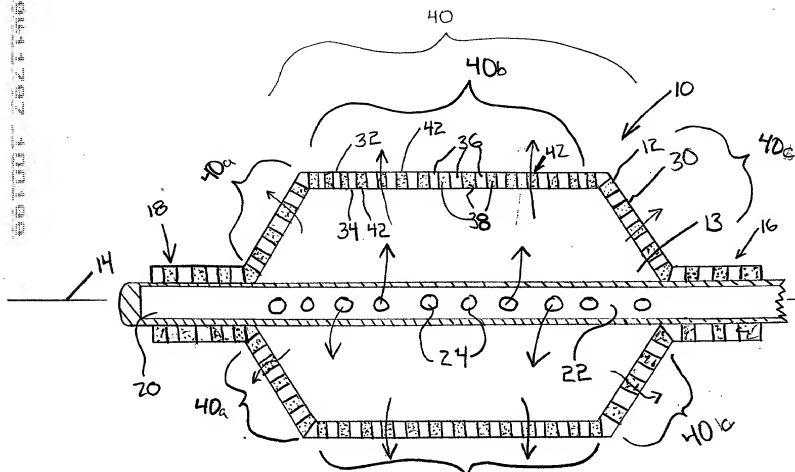


FIG. 2 40b

FIG. 3

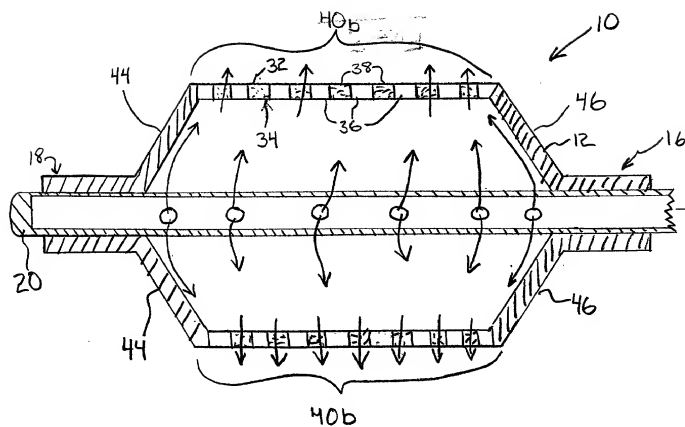
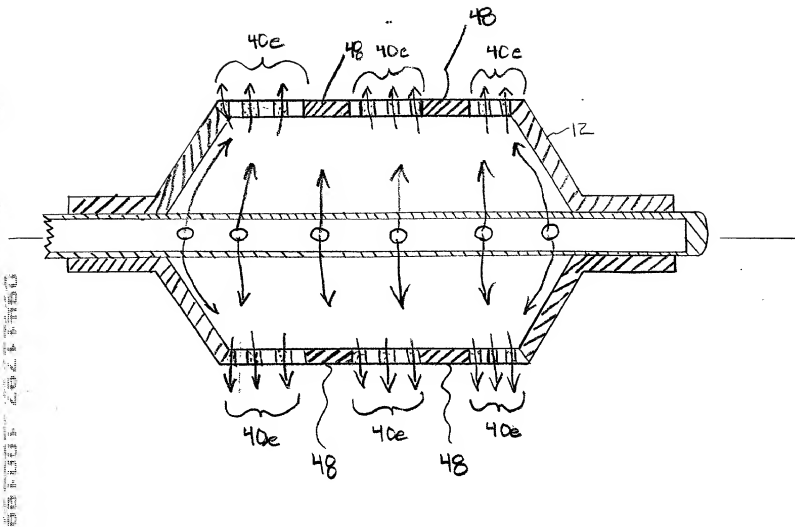


FIG. 4



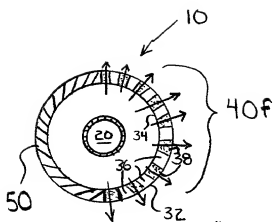


FIG. 5

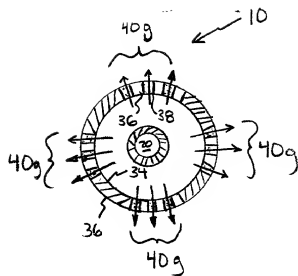


FIG. 6

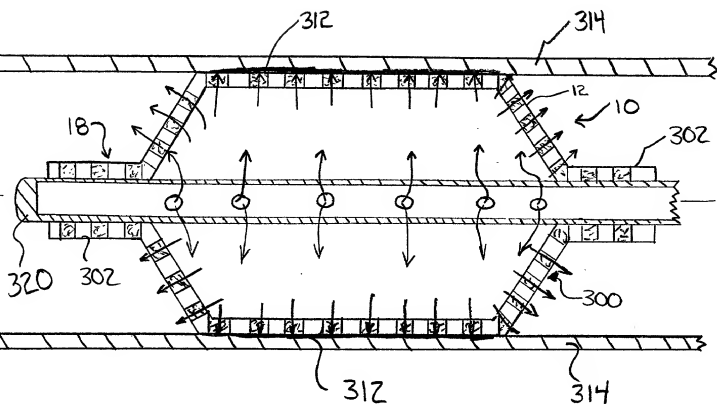


FIG. 12

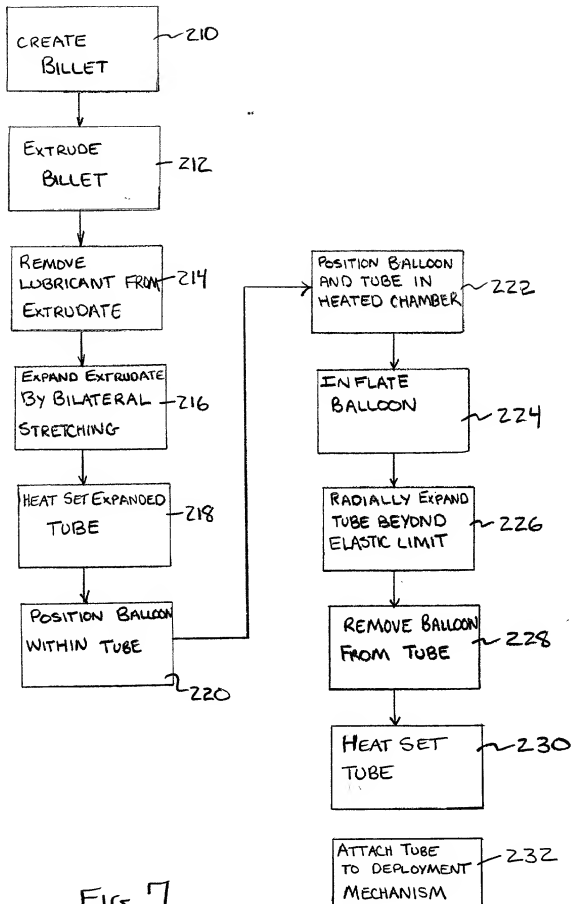


FIG. 7

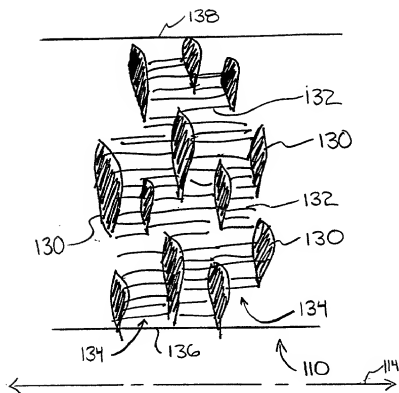


FIG. 8

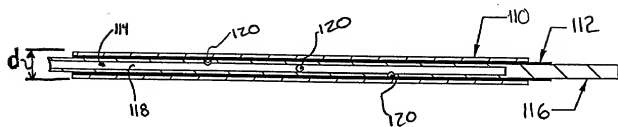


FIG. 9A.

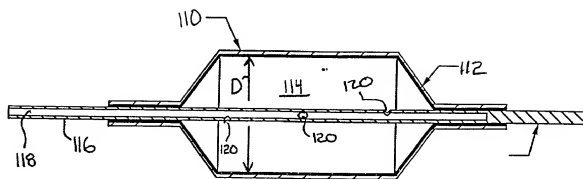


FIG. 9B

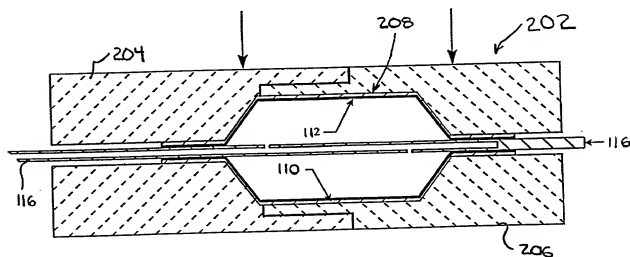
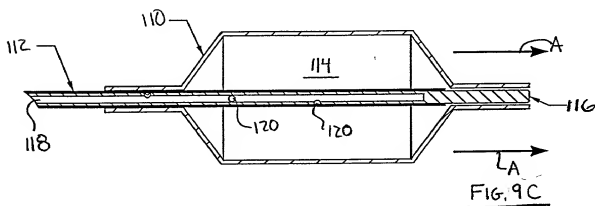


FIG. 11

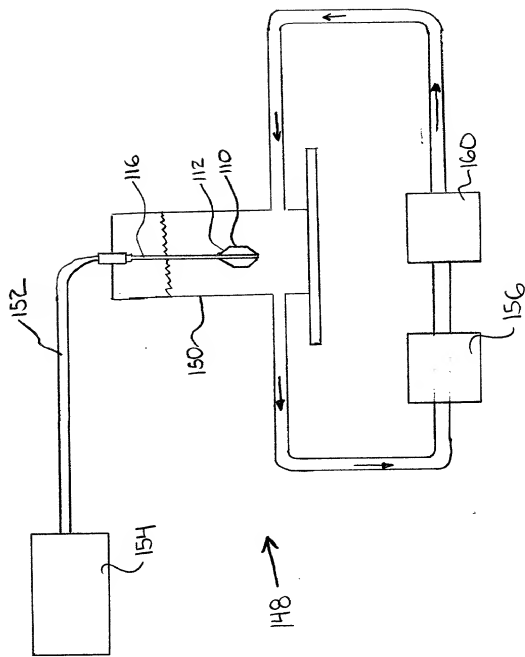
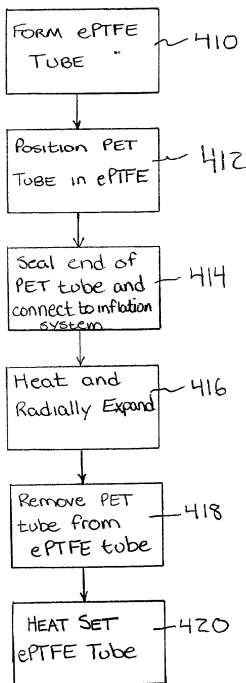


FIG. 10

FIG. 13



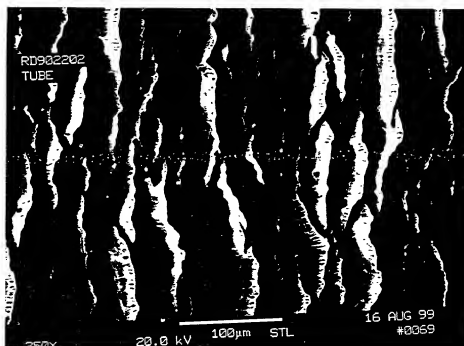


FIG. 14A

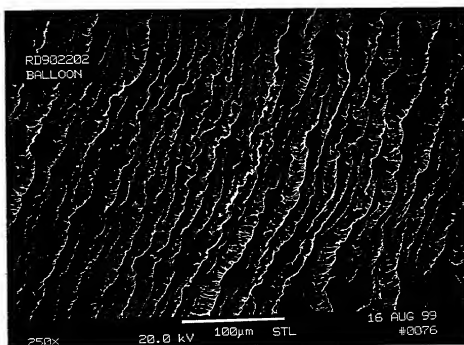


FIG. 14B

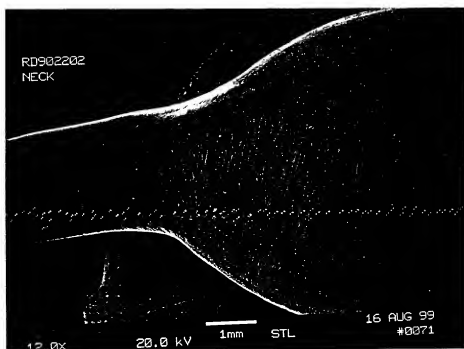


FIG. 14C

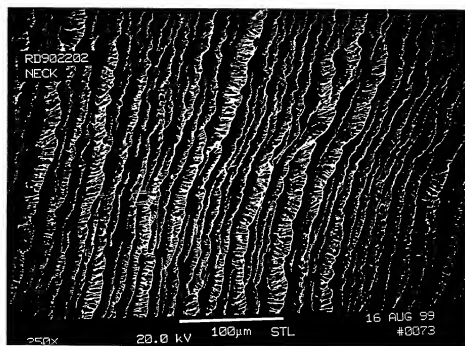


FIG. 14D

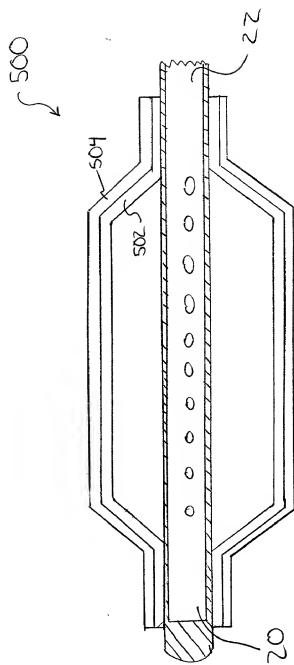


FIG. 15

Attorney's
Docket
Number ATA-257

Declaration, Petition and Power of Attorney for Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

EXPANDABLE FLUOROPOLYMER DEVICE FOR DELIVERY
OF THERAPEUTIC AGENTS AND METHOD OF MAKING

the specification of which

(check one)

X is attached hereto.

was filed on _____ as

Application Serial No. _____

and was amended on _____
(if applicable)

I do not know and do not believe that the subject matter of this application was known or used by others in the United States or patented or described in a printed publication in any country before my invention thereof, or patented or described in a printed publication in any country or in public use or on sale in the United States more than one year prior to the date of this application, or first patented or caused to be patented or made the subject of an inventor's certificate by me or my legal representatives or assigns in a country foreign to the United States prior to the date of this application on an application filed more than twelve months (six months if this application is for a design) before the filing of this application; and I acknowledge my duty to disclose information of which I am aware which is material to the examination of this application, that no application for patent or inventor's certificate on the subject matter of this application has been filed by me or my representatives or assigns in any country foreign to the United States, except those identified below, and that I have reviewed and understand the contents of the specification, including the claims as amended by any amendment referred to herein.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

CLAIM OF BENEFIT OF EARLIER FOREIGN APPLICATION(S)

I hereby claim priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below, and have also identified below any foreign application(s) for patent or inventor's certificate filed by me on the same subject matter having a filing date before that of the application(s) from which priority is claimed.

Check one:

☒ no such applications have been filed.

☐ such applications have been filed as follows

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

Country	Application Number	Date of Filing (month,day,year)	Priority Claimed Under 35 USC 119
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

CLAIM FOR BENEFIT OF U.S. PROVISIONAL APPLICATION(S)

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

60/117,152

(Application Serial No.)

January 25, 1999

(Filing Date)

(Application Serial No.)

(Filing Date)

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S)

I hereby claim the benefit under Title 35, United States Code, §120 of any earlier United States application(s) or PCT international application(s) designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the earlier application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date(s) of the earlier application(s) and the national or PCT international filing date of this application. As to subject matter of this application which is common to my earlier application(s), if any, described below, I do not know and do not believe that the same was known or used by others in the United States or patented or described in a printed publication in any country before my invention thereof, or patented or described in a printed publication in any country or in public use or on sale in the United States more than one year prior to the date(s) of said earlier application(s), or first patented or caused to be patented or made the subject of an inventor's certificate by me or my legal representatives or assigns in a country foreign to the United States prior to the date(s) of said earlier application(s) on an application filed more than twelve months (six months if this application is for a design) before the filing of said earlier application(s); and I acknowledge that no application for patent or inventor's certificate on said subject matter has been filed by me or my representatives or assigns in any country foreign to the United States except those identified herein.

(Application Serial No.)

(Filing Date)

(Status)
(patented,pending,aband.)

(Application Serial No.)

(Filing Date)

(Status)
(patented,pending,aband.)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

W. Hugo Liepmann	Reg. No. 20,407	Catherine J. Kara	Reg. No. 41,106
James E. Cockfield	Reg. No. 19,162	Faustino A. Lichauco	Reg. No. 41,942
Thomas V. Smurzynski	Reg. No. 24,798	Jeanne M. DiGiorgio	Reg. No. 41,710
Ralph A. Loren	Reg. No. 29,325	Megan E. Williams	Reg. No. 43,270
Giulio A. DeConti, Jr.	Reg. No. 31,503	Nicholas P. Triano III	Reg. No. 36,397
Ann Lampert Hammitte	Reg. No. 34,858	Peter C. Lauro	Reg. No. 32,360
Elizabeth A. Hanley	Reg. No. 33,505	Reza Mollaaghhaba	Reg. No. 43,810
Amy E. Mandragouras	Reg. No. 36,207	Timothy J. Douras	Reg. No. 41,716
Anthony A. Laurentano	Reg. No. 38,220	John L. Welch	Reg. No. 28,129
Jane E. Remillard	Reg. No. 38,872	DeAnn F. Smith	Reg. No. 36,683
Jeremiah Lynch	Reg. No. 17,425	William D. DeVaul	Reg. No. 42,483
Kevin J. Canning	Reg. No. 35,470	David J. Rikkers	Reg. No. 43,882
David A. Lane, Jr.	Reg. No. 39,261	Chi Suk Kim	Reg. No. 42,728

Send Correspondence to Kevin J. Canning at **Customer Number: 000959** whose address is:

Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109

Direct Telephone Calls to: (name and telephone number)

David A. Lane, Jr. (617) 227-7400

Wherefore I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Steve A. Herweck	
Inventor's signature	Date
Residence 12 Lansing Drive, NH 03062	
Citizenship United States of America	
Post Office Address (if different)	

Full name of second inventor, if any Peter H. Gingras	
Inventor's signature	Date
Residence 24 Blossom Road, Windham, NH 03087	
Citizenship United States of America	
Post Office Address (if different)	

Full name of third inventor, if any Paul Martakos	
Inventor's signature	Date
Residence 1 Regis Drive, Pelham, NH 03076	
Citizenship United States of America	
Post Office Address (if different)	

Full name of fourth inventor, if any Theodore Karwoski	
Inventor's signature	Date
Residence 61 Hannah Drive, Hollis, NH 03049	
Citizenship United States of America	
Post Office Address (if different)	